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| EXAMINER | |
|---|---|
| RAMACHANDRAN, UMAMAHESWARI | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,133 | DIDRIKSEN ET AL. | |
| | Examiner | Art Unit | |
| | UMAMAHESWARI RAMACHANDRAN | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4,7,8,10,11,13-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 7-8, 10-11, 13-17, 19, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 1/10/2008. Claims 1, 3, 4, 7, 8, 11 have been amended, claims 2, 5, 6, 7, 8, 11 have been cancelled. Claims 1, 3, 4, 7, 8, 10, 11, 13-17, 19, 20 are currently pending and are being examined on the merits herein.

### Response to Remarks

Applicants' arguments regarding the rejection of claims 1, 3, 4, 1, 3-5 under 35 U.S.C. 112, first paragraph have been fully considered and found not persuasive. Applicants' arguments regarding the rejection of Claims 1, 3-14, 19 under 35 U.S.C. 103(a) as being unpatentable over Coppen (U.S. 6,191,133) in view of Lowe (U.S. 6,506,780) and further in view Moltzen et al. (U.S. 2003/0181445, effective filing date, July 19 2001) and further in view of Mork et al. (U.S. 2005/0288355, effective filing date, Jun 19 2003), rejection of claims 13-16, 20 and claim 17 under U.S.C 103(a) have been fully considered and found not persuasive. Applicants' arguments have been addressed below. Applicants' amendments necessitated the modified rejections presented in this office action. Hence the action is made final.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for serotonin analysis and measurement of serotonin

levels with citalopram and glycine transport inhibitor NFPS (specification, page 25-26) does not reasonably provide enablement for disorders such as depression, anxiety disorders and other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse as listed in specification (see abstract). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

**(1) The nature of the Invention:**

The rejected claims are drawn to a method of treating a disorder selected from depression, anxiety disorders and other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound .

**(2) Breadth of the claims:**

Claims 1, 3-4 are broad and is drawn to a method of treating a disorder selected from depression, anxiety disorders, other affective disorders (as listed in the specification) comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claim.

**(3) Guidance of the Specification:**

The guidance given by the specification is for a method of for serotonin analysis and measurement of serotonin levels with citalopram and glycine transport inhibitor NFPS (specification, page 25-26).

**(4) Working Examples:**

The example in the specification provides methods for serotonin analysis and measurement of serotonin levels in hippocampus.

**(5) The relative skill of those in the art:**

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

**(6) The predictability of art:**

Claims 1, 3-4 is drawn to a method of treating a disorder selected from depression, anxiety disorders, other affective disorders (as listed in the specification) comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound. Claims 1, 3-5 are so broad and there is a high degree of unpredictability involved. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

**(7) The Quantity of Experimentation Necessary:**

In order to practice the above claimed invention, one of skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system for the treatment of every single disorder listed in claim1 with a combination of citalopram and escitalopram with a GlyT-1 inhibitor combination. If unsuccessful, one of skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating the disorders listed in claim1. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that “a patent is not

a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement in a method of treating a disorder listed in claim 1 with serotonin reuptake inhibitors selected from citalopram and escitalopram and GlyT-1 inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the

presence or absence of working examples; and (8) the quantity of experimentation necessary.

**(1) The nature of the Invention:**

The rejected claims are drawn to a method of treating a disorder selected from depression, anxiety disorders, and other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound.

**(2) Breadth of the claims:**

Claims 1, 3-5 are broad and is drawn to a method of treating a disorder selected from depression, anxiety disorders, and other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claim.

**(3) Guidance of the Specification:**

The guidance given by the specification is for a method of for serotonin analysis and measurement of serotonin levels with citalopram and glycine transport inhibitor NFPS (specification, page 25-26).

**(4) Working Examples:**

The example in the specification provides methods for serotonin analysis and measurement of serotonin levels in hippocampus with citalopram and glycine transport inhibitor NFPS. The specification does not provide examples with any other SSRI and GlyT-1 inhibitor combination in a method of treating a disorder or in serotonin analysis or measurement of serotonin.

**(5) The relative skill of those in the art:**

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

**(6) The predictability of art:**

Claims 1, 3-5 is drawn to a method of treating a disorder selected from depression, anxiety disorders, other affective disorders comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound. The method of treatment comprises the administration of an SSRI and a GlyT-1 inhibitor in combination and there is a high degree of unpredictability involved. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

**(7) The Quantity of Experimentation Necessary:**

In order to practice the above claimed invention, one of skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system for the treatment of serotonin reuptake inhibitor selected from citalopram and escitalopram and GlyT-1 inhibitor combination for every single disorder selected from depression, anxiety disorders, other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating the disorders listed in claim 1 administering SSRI selected from citalopram and escitalopram and GlyT-1 combination therapy. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 7, 8, 10, 11, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coppen (U.S. 6,191,133) in view of Lowe (U.S. 6,506,780) and further in view Moltzen et al. (U.S. 2003/0181445, effective filing date, July 19 2001) and further in view of Mork et al. (U.S. 2005/0288355, effective filing date, Jun 19 2003).

Coppen teaches specific formulation for the treatment of depression comprising serotonin reuptake inhibitors (SSRI) such as citalopram (col.8, example 5). The reference teaches a method of treating depression in a patient comprising administering to the patient a therapeutically effective amount of an anti-depressive compound selected from the class of compounds comprising serotonin reuptake inhibitors and teaches citalopram as one of the anti-depressants (col. 10, claims 6-10). The reference teaches SSRI inhibitors and the second agent folate in the same dosage unit forms as tablets and further teaches that SSRI can be administered simultaneously with another agent such as folate (col. 10, claim 10).

The reference does not teach a GlyT-1 inhibitor in the composition comprising serotonin reuptake inhibitor for the treatment of depression.

Lowe et al. teach that compounds that exhibit activity as inhibitors of glycine type I transporter are useful in the treatment of depression (col. 1, lines 10-14). The

reference further teaches a pharmaceutical composition comprising the GlyT-1 inhibitor and a method of treating a disorder or condition such as psychosis, psychotic disorders, and depression etc. administering GlyT-1 inhibitor compounds (col. 33-36, claims 1-16).

The reference does not teach the elected species N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine as the GlyT-1 inhibitor in the composition in a method of treating depression.

Moltzen et al. teaches a pharmaceutical composition comprising GlyT-1 inhibitor such as N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine (elected species) in a therapeutically effective amount with one or more of pharmaceutically acceptable carrier/diluents (para 0084, col. 11, claim 9) with a inhibition of glycine below 20000 nM (IC 50 in the glycine uptake test is 470, p10, Table). The reference further teaches a method of treatment of psychoses, comprising administering to a patient the above said pharmaceutical composition (col. 11, claims 10, 11).

The references do not teach a method for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor in a person comprising administering a serotonin reuptake inhibitor and a GlyT-1 inhibitor compound.

Mork et al. teach a method of augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor comprising administering a second agent such as GABA receptor antagonist in a method of treatment of disorders such as depression (p 9, col. 2, claims 1-4). The reference also teaches in the background there is the delay in therapeutic effect of SSRIs (para 004) and augmentation therapy is done in order to cope with non-response to SSRI's (para 005, 003).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer serotonin reuptake inhibitors (SSRI) such as citalopram (elected species) along with a GlyT-1 inhibitor in a method of treatment of depression. The motivation to do so is provided by Coppen, Lowe, Moltzen and Mork et al. The references in combination teach both SSRI and GlyT-1 inhibitor in a method of treatment of depression. Coppen specifically teaches the benefits of the elected species citalopram in the treatment of depression. Moltzen teach GlyT-1 inhibitor (elected species) in a method of treatment of psychoses and Lowe exemplifies the use of GlyT-1 inhibitors in a method of treatment of depression. Finally Mork teaches the use of citalopram in depression disorder treatment and further teaches the beneficial effects of combination therapy to augment or to provide a faster onset of the therapeutic effect of an SSRI by adding a second agent. The Moltzen reference does not specifically teach the elected species of GlyT-1 inhibitor (N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine) in a method of treatment of depression but teaches the elected compound in a method of psychosis. Stedman medical dictionary defines psychosis as 'A severe mental disorder, with or without organic damage, characterized by derangement of personality and loss of contact with reality and causing deterioration of normal social functioning'. It is known that people who have psychosis often are depressed and psychotic depression is a type of depression disorder. One of ordinary skill in the art would have been motivated to use GlyT-1 inhibitor (N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine, the elected species) in a method of treatment of depression because Moltzen teaches the compound as GlyT-1 inhibitor

and in a method of treatment of psychoses and Lowe teaches the use of GlyT-1 inhibitors in a method of treatment of depression. Hence one of ordinary skill in the art would have been motivated to combine citalopram and a GlyT-1 inhibitor in a composition to treat a disorder such as depression because the teachings show the therapeutic benefits and safety of such drugs in the treatment of depression. The examiner respectfully points out the following from MPEP 2144.06: "It is **prima facie obvious** to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their, having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069,-1072 (CCPA 1980).

One of ordinary skill in the art at the time of the invention would have been motivated to have added another agent such as GlyT-1 inhibitor to SSRI to provide augmentation and or to provide faster onset of therapeutic effect of SSRI because it can offset the delay in the therapeutic effects of SSRI's or to cope up with non-response to SSRI's as taught by Mork et al.

Claims 13-16, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coppen (U.S. 6,191,133) in view of Lowe (U.S. 6,506,780) and further in view Moltzen et al. (U.S. 2003/0181445, effective filing date, July 19 2001) and further in view of Mork et al. (U.S. 2005/0288355) as applied to claims 1, 3, 4, 7, 8, 10, 11, 19 above and further in view of Carlson et al. (U.S. 6,649,614).

Coppen, Lowe, Moltzen and Mork et al.'s teachings discussed as above.

The references do not teach the pharmaceutical composition adapted for sequential administration or the active ingredients in discrete dosage forms.

Carlson et al. teach the treatment of depression comprising administering a combination of an antidepressant such as SSRI and an NK-1 receptor antagonist (see abstract, col.2, line 49). The reference teaches citalopram as one of the antidepressants in the treatment (col.6, line 26). The reference teaches the composition in unit dosage forms such as tablets, pills etc (col. 34, lines 43-45) and further teaches that in combination therapy the compounds may be in the same pharmaceutically acceptable carrier for simultaneous administration or in separate dosage forms for sequential administration (col. 3, lines 61-67).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have provided a pharmaceutical composition comprising SSRI and a GlyT-1 inhibitor adapted for sequential administration or the active ingredients in discrete dosage forms for the treatment of depression. One of ordinary skill in the art would have been motivated to do so is by the teachings of Carlson. The reference teaches a method of treatment of depression comprising a composition in unit dosage forms, separate dosage forms and further teaches the mode of administration (sequential, simultaneous). Hence one of ordinary skill in the art would have expected similar success and it is also part of routine experimentation to try various modes of administration and dosage forms. The examiner respectfully points out the following from MPEP 2144.05: “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coppen (U.S. 6,191,133) in view of Lowe (U.S. 6,506,780) and further in view Moltzen et al. (U.S. 2003/0181445, effective filing date, July 19 2001) and further in view of Mork et al. (U.S. 2005/0288355) as applied to claims 1, 3-12, 19 above and further in view of Gupta et al. (US 2005/0014743), Remington's: the Science and Practice of Pharmacy, Nineteenth edition, vol. 1, p 806.

Coppen, Lowe, Moltzen and Mork et al.'s teachings discussed as above.

The references do not teach a kit comprising a serotonin reuptake inhibitor, GlyT-1 inhibitor and optionally a pharmaceutical carrier.

Gupta et al. teach a method of treatment of depression using SSRI such as citalopram in a combination therapy and further teaches a kit comprising SSRI and other active agents (See Abstract, p 11, para 0242) for the treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a kit comprising SSRI and GlyT-1 inhibitor. One of ordinary skill in the art

would have been motivated to provide a kit because Gupta et al. teaches one comprising SSRI and other active agents and providing kits helps patients to take the drugs with ease as per the instructions in the kit.

Remington's: the Science and Practice of Pharmacy, Nineteenth edition, vol. 1, p 806 teaches the inclusion of package and insert including the "indications and use" of the pharmaceutical composition is mandated by 21 CFR 201.57.

One of ordinary skill in the art would have been motivated to include the packaging and the insert because they have been mandated by the law as taught by Remington's.

The examiner respectfully points out the following from MPEP 2106.01: "Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." In re Ngai (70 USPQ2d 1862).

**Response to Arguments**

(1) Rejection under 35 USC 112, first paragraph (enablement)

Applicants' argue that a person of ordinary skill in the art would readily understand that an elevation in extracellular levels of serotonin would be efficacious in treating depression, anxiety disorders and other affective disorders. In response, the instant claims are broad and are directed to a method of treating depression, anxiety disorders and other affective disorders that include generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and

obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse as listed in specification (see abstract) in a drug combination therapy comprising administering to the person a serotonin reuptake inhibitor selected from citalopram and escitalopram and a GlyT-1 inhibitor compound. While the state of the art is relatively high with regard to the treatment of depression with specific agents, the unpredictability observed with single agents is compounded when a combination of agents is used. Combination therapies, while desirable, are a hit or miss proposition. In many cases, cross effects and treatment load can result in lower effectiveness for the combinations, than either treatment alone. Dresser (CMAJ Feb 23, 1999, 160(4), teach that in choosing the right antidepressant for an individual it is imperative to consider carefully any concurrently prescribed medications. The selective serotonin reuptake inhibitors are known to interact with many medications, including benzodiazepines, some antipsychotics, tricyclic antidepressants and antihistamines (p 470, col. 1, para 2). The reference further teach that the physicians who prescribe must well be acquainted not only with the adverse effects commonly experienced when the drugs are given in isolation, but also with their particular drug-drug interaction profiles (p 470, col.2, lines 2-5). Trindade et al. (CMAJ, Nov 17, 1998, 159(10) teach the adverse effects associated with selective serotonin reuptake inhibitors with tricyclic depressants. The study clearly teaches the adverse effects associated with SSRI agents. Also, an article on celexa (citalopram) teaches that celexa when taken with other medications that raise serotonin levels may cause serious interactions (see p 1, http://www.drugstore.com/qxa1190_333181_

sespider- do_other_therapies_interact_with_celexa.html). It is clear that in a drug combination therapy, the drug-drug interactions and adverse effects associated in the combination therapy has to be studied for the treatment. Thus, when two (or more) agents are used, even more additional empirical testing is required, again with no a priori expectation of success. Hence one skilled in the art would have to test citalopram or escitalopram with every single GlyT-1 inhibitor of prospective embodiments for depression, anxiety disorders and other affective disorders and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as it is claimed in its current scope. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating the disorders listed in claim 1 administering SSRI selected from citalopram and escitalopram and GlyT-1 combination therapy.

(2) Rejection under 35 USC 103 as being unpatentable over Coppen (U.S. 6,191,133) in view of Lowe (U.S. 6,506,780) and further in view Moltzen et al. (U.S. 2003/0181445,) and further in view of Mork et al. (U.S. 2005/0288355).

Applicants' argue that none of the prior art teach that GlyT-1 inhibitors alone or in combination with any other drug can elevate extracellular serotonin levels and thus be useful in the treatment of depression. In response, the claims of the instant application are directed to a method of treating depression, anxiety disorders, and other affective disorders comprising administering citalopram or escitalopram and GlyT-1 inhibitor. There is no limitation in the claim of the instant application that GlyT-1 inhibitors alone

or in combination with any other drug can elevate extracellular serotonin levels. Applicants' argue that it would not have been obvious to the person skilled in the art to combine selective SSRI inhibitors with GlyT inhibitors. In response, Coppen teach the usefulness of citalopram in depression, Moltzen teach GlyT-1 inhibitor (elected species) in a method of treatment of psychoses and Lowe exemplifies the use of GlyT-1 inhibitors in a method of treatment of depression. It is known that people who have psychosis often are depressed and psychotic depression is a type of depression disorder. One of ordinary skill in the art would have been motivated to use GlyT-1 inhibitor (N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine, the elected species) in a method of treatment of depression because Moltzen teaches the compound as GlyT-1 inhibitor and in a method of treatment of psychoses and Lowe teaches the use of GlyT-1 inhibitors in a method of treatment of depression. Hence one of ordinary skill in the art would have been motivated to combine citalopram and a GlyT-1 inhibitor in a composition to treat a disorder such as depression because the teachings show the therapeutic benefits and safety of such drugs in the treatment of depression.

The examiner notes the applicants' comments regarding the restriction of election of species. Applicants' elected depression, citalopram and N-{3-[5-Chloro-l-(4-chloro-phenyl)-indan-l-yl]-propyl}-N-methyl-alanine as the species and the election is maintained for all the claims of the instant invention. Moltzen et al. teach the elected compound as a GlyT inhibitor and hence the search and examination has been done to the full scope of the claims.

## Conclusion

No Claims are allowed.

Applicant's amendment necessitated the modified rejections presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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